SmithKline Beecham
Pharmaceuticals

October 22, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Draft FDA Guidance on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action
Docket No. 99D-1738

Dear Sir/Madam:

Enclosed, please find our comments on this guidance document. We hope that these comments will help the agency in designing its final guidance for industry.

The draft guidance according to the Notice issued at the time of the publication is intended to provide guidance for industry on planning studies to measure bioavailability and bioequivalence studies in support of new drug applications (NDA's) or abbreviated new drug applications (ANDAs) for nasal aerosols (metered-dose inhalers) and nasal sprays (metered-dose spray pumps) for local action.

Thank you for the opportunity to evaluate and respond to this draft guidance.

Sincerely,

Debra Hackett

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99D-1738 C15

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Draft FDA Guidance on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action
Docket No. 99D-1738

General Comments

1. Population and Individual BE: The guidance is confused by reference throughout, when discussing in vitro BE, to the concepts of population and individual bioequivalence which are themselves the subject of a draft guidance yet to be finalised (and then only in the context of *in vivo* BE studies). It would simplify this guidance enormously to simply cross-refer to currently accepted bioequivalence guidelines, making it clear that new bioequivalence guidelines may be applied in this context when they are finalised.

Specific Comments

INTRODUCTION

p.2. para 1: The guidance is very specific about the classes of intranasal product covered and is not applicable for other classes of intranasal drugs which will be developed in the future.

BACKGROUND

p.4, 1. Local Delivery BA/BE Concepts, para 1: The sentence beginning "An *in vivo* systemic exposure.." should make it clear that this is only expected if a drug assay is achievable.

VI. BIOAVAILABILITY & BIOEQUIVALENCE: CLINICAL STUDIES FOR LOCAL DELIVERY

p.17, B. Clinical Study Endpoints: Statistical analysis of change from baseline measurements should be avoided in favour of analysis of covariance using the absolute values of each measure.

p.18, 1. Traditional Treatment Study: The definition needs to be more clearly laid out with respect to which formulations are being evaluated in this study design and what is the purpose of the two-week run-in period. Since the efficacy endpoint of total nasal symptom scores (TNSS) will be determined at least twice daily, clarification is required as to how these measures should be combined to assess bioequivalence (this comment applies also to other study designs).

p.18, 2. Days in Park Study: How variation in response rate between individuals etc. is accounted for in this design requires clarification. Also, some clarification is required as to whether all subjects are to be studied on the same day. If not, then the study design needs to ensure that subjects on studied on similar days (with respect to allergen exposure) and that there is a balance between the groups of subjects being studied on each day.

pp.19, 3. Environmental Exposure Unit: With an adequate wash-out period e.g. 14 days, the EEU allergen challenge study could be conducted to a cross-over design, with the anticipated benefit of reducing sample size.

VII BIOAVAILABILITY AND BIOEQUIVALENCE

p.19, PK Systemic Exposure Studies, para 1: The primary endpoints for BE assessment (presumably Cmax and AUC) should be stated.

pg 20, B. BE Study Endpoints for corticosteriods : Since the endpoint may be serum cortisol levels collected every 4 hours over a 24 hour period, there could be six actual values for each asessment period. It should be clarified how these are to be summarised/collapsed into one endpoint.

p.20, PK Systemic Exposure Studies, para 2, last sentence: It should state "A pilot study or data from previous studies is recommended..."

p.21, B. BE Study Endpoints for Corticosteroids, last sentence: Clarification is required regarding the method of baseline adjustment prior to statistical analysis. SB recommend ANCOVA rather than analysis of change from baseline.

p.21, D. Clinical Study Designs and Subject Inclusion Criteria: A double-dummy approach be considered for incorporation in these designs.

IX STATISTICAL ANALYSIS

p.22, IX.A. *In Vitro* BE Data: Are the "percent CV's" to be reported derived on the arithmetic scale or on the log scale? (ii) The proposed analysis makes sense, being that for a nested design for each formulation. Assuming:

b (=3) batches;
c (=10) canisters per batch;
s (=3) lifestages per canister;

then the ANOVA table would be:

	Degrees of freedom	
Expected Mean Squares		
Between batches	(b-1)	2
LT2 + s.CT2 + sc.BT2		
Between canisters within batches	b(c-1)	27
LT2 + s.CT2		
Between lifestages within canisters	bc(s-1)	60
LT2		
TOTAL	bcs-1	89

As well as the overall mean, the following mean values are also requested:

	Lifestages (from:)		
Batch	Beginning	Middle	End
1	x	x	x
2	x	x	x
3	x	x	x
Overall	x	x	x

p.22, IX.B In vitro BE Data: Nonprofile Analyses using a confidence interval approach: It is not clear in section 2, how the BE criterion described under IX.B applies to the multinomial situation, ie how Rd is calculated from MN(100,PR), FBR and FCR for the reference data (and similar definition for test data). Further comments for the derivation of Rd based on the chi-square 'triplet' approach, which is described in more detail, are given below under Appendix A.

p.28, E. *In vivo* BE Data: Categorical Endpoints: SB would like to see the wording of this section before the guidance is finalised.

p.28, *In vivo* BE PK Systemic Exposure Studies: For completeness, there should be a sub-heading here with a brief statement simply cross-referring to existing bioequivalence guidelines.

p.32 Decision Tree for Product Quality: The mention in the flow chart of "Clinical study for systemic absorption" is confusing, since this guidance is intended to cover only intranasal products for local action.

p.32, Decision Tree for Product Quality : The order of the studies in the final 2 boxes of the flow chart are a little misleading as "In vitro studies" appear last in the list when in fact they will probably be conducted before "Clinical study for local delivery ....".

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